



Viewpoints

Human immunodeficiency virus and the liver: The impact of coinfection with hepatotropic viruses

Leonor Huerta^a, Julio Y. Anaya-Covarrubias^{b,c}, Nora A. Fierro^{a,b,c,*}^a Department of Immunology, Biomedical Research Institute, National Autonomous University of Mexico, Mexico^b Department of Molecular Biology in Medicine, Civil Hospital of Guadalajara "Fray Antonio Alcalde", Mexico^c Health Sciences Center, University of Guadalajara, Mexico

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ABSTRACT

Human immunodeficiency virus (HIV) predisposes for liver damage during coinfection with hepatitis E virus (HEV) and increases the replication of hepatitis C virus (HCV). HIV-hepatitis B virus (HBV) coinfections are common. In Mexico, hepatotropic viruses are major causative agents of liver disease. However, information on HIV coinfections is limited in the country.

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1. Introduction

Liver disease is a common feature of untreated and antiretroviral-treated human immunodeficiency virus (HIV) infection. Currently, liver disease represents the second cause of mortality on acquired immune deficiency syndrome (AIDS) accounting for 14–18% of all deaths, and on 50% of deaths among hospitalized HIV-infected patients in antiretroviral therapy (ART).

HIV itself may affect the liver. In HIV-monoinfected patients, high HIV loads constitute an independent risk factor for chronic steatosis and elevation of alanine aminotransferase (ALT). A detectable HIV load combined with aspartate aminotransferase (AST)-to platelet ratio index (APRI) greater than 1.5 is a risk factor of liver disease development and precise for significant fibrosis [1].

The liver may have a major role in filtration and clearance of HIV from blood, and thus it may concentrate infectious virus and viral products [2]. Whereas it is found primarily in hepatic macrophages, evidences show that HIV can also be internalized by hepatocytes, where it may remain infectious and even undergo low level of replication [3]. After ART, persistence of HIV seems associated with a

deficient penetration of drugs in several tissues, including the liver. Moreover, the long-lasting presence of HIV in the liver stimulates chronic inflammation and fibrogenesis [1]. Low local concentrations of drugs may promote low level of HIV replication, which has been shown to be sufficient to favor the expression of other hepatic virus antigens. In fact, it is accepted that hepatotropic viruses greatly contribute to liver injury in HIV-infected patients [2].

Until few years ago, hepatitis C virus (HCV) and hepatitis B virus (HBV) were considered as the main hepatotropic viruses related to chronic liver injury. Today, it is understood that hepatitis E virus (HEV), the leading causative agent of acute hepatitis worldwide, is also able to induce chronic liver infections in immunocompromised individuals including those HIV-infected [4].

With the main goal of viral hepatitis eradication in 2030 endorsed by the World Health Organization, identification of the current global situation of coinfections with HIV and hepatotropic viruses is priority, particularly in geographical regions where hepatic diseases represent a major concern.

In Mexico, liver injury constitutes the fourth cause of death in adults (<http://www.conapo.gob.mx> <http://pda.salud.gob.mx/cubos/>). However, there are few studies on HIV/HBV and HIV/HCV coinfections and the study of HIV/HEV coinfection has not been documented in the country. The design of better diagnostics strategies on the basis of understanding the epidemiology and pathophysiology of HIV coinfection with hepatotropic viruses is necessary.

* Corresponding author at: Departamento de Inmunología, Instituto de Investigaciones Biomédicas, Universidad Nacional Autónoma de México, 045210. Ciudad de México, Mexico.

E-mail address: noraalma@iibiomedicas.unam.mx (N.A. Fierro).

2. HIV: co-infection with HBV and HCV

Mexico has the highest rate of death in Latin America due to liver cirrhosis. Alcohol liver disease and HCV are the most frequent causes of cirrhosis in the country, followed by HBV infections (<http://www.inegi.org.mx/est/contenidos/proyectos/registros/vitales/mortalidad/tabulados/ConsultaMortalidad.asp>). According to the local government health agency in Mexico (Secretaría de Salud, SSA in Spanish) from 1983 to 2018 a total of 196,227 HIV-AIDS cases have been reported (<http://www.gob.mx/censida>). Globally, it is accepted that a high proportion of HIV+ patients live with HCV. In northern Mexico, a low seroprevalence of HIV/HCV coinfection has been reported [6]. In spite that, the analysis of HIV-infected patients with liver fibrosis has shown an accelerated liver disease in conditions of HCV coinfection and, the abuse of alcohol consumption significantly enhance the risk of advanced fibrosis and cirrhosis in HIV-HCV coinfection in distinct populations worldwide [1]. Thus, deeper studies in geographical regions where liver disease is common are necessary to define the exact role of HIV/HCV coinfection on hepatic function.

It is accepted that a 10% of HBV+ patients are coinfecting with HIV worldwide and, liver-related mortality is significantly higher in HIV-HBV-coinfecting individuals than in those infected with either HIV or HBV alone. In addition, occult hepatitis B (OBI) defined as HBV infection with undetectable levels of HBsAg, has been found in immunosuppressed patients. In Mexico, OBI has been documented in HIV-infected subjects [7] and, an incidence of 29% of HIV/HBV coinfection related to advanced liver disease in low income populations from Mexico has been documented [8]. The study of HIV in coinfection with HBV and HCV is particularly relevant by taking into account that these viruses share transmission mechanisms.

3. HIV and HEV

HEV represents a major public health problem as the main promoter of acute viral hepatitis worldwide and in the context of immunosuppression it may cause chronic infections and promote liver damage. A major number of the HEV-related chronic infections described at the date correspond to patients receiving organs and, limited information in coinfection with HIV is available.

The global prevalence of HIV/HEV coinfection is not well established, with variable rates that depend on the geographical area and study population, as well as the HEV detection analysis used (PCR, immunoblot or ELISA). For example, when considering the prevalence of serum IgG antibodies against HEV (anti-HEV) in patients with HIV, it varies between 1% and 45% of the population. In addition, cases have been reported where PCR detection is positive for HEV, but negative for IgG and/or IgM anti-HEV probably due to the deficiency of antibody production as a result of HIV infection [9].

HEV has a high incidence in developing countries, where fecal-oral, zoonosis, person-to-person contact and vertical transmission may occur [5]. In Mexico, SSA does not report HEV+ cases. However, we have recently reported HEV genotype 1 circulation in western Mexico [10] and genotypes 2 and 3 have been previously reported from human and animal sources respectively in the country [5].

Studies from different geographical regions have characterized risk factors such as the use of drugs, sexual orientation, breeding and/or consumption of pork, CD4 lymphocyte count in the blood, viral load of HIV, use of ART, stage of AIDS, coinfection with HAV, HBV, HCV, cirrhosis and age. Within these factors, CD4+ lymphocyte counts of <100–200 cells/mm³, a severe immunosuppression, is the factor mostly associated with HEV infection in HIV-infected patients worldwide [9]. However, the study of specific regions, including Mexico, in order to establish the risk factors for HIV/HEV coinfection is still in progress.

4. Remarks

Over the last years, the epidemiological scenarios of HBV, HCV, HEV and HIV have been changing, and accurate data regarding the prevalence of infection/co-infection rates is still limited. In Mexico, among HIV infected patients, particularly in those with a low socioeconomic status, viral hepatitis in coinfection with HIV may play a central role in the epidemiological scenarios of liver injury. However, limited studies on HIV/HBV and HIV/HCV coinfections are available. In addition, given HEV is not commonly tested as a causative agent of liver disease in Mexico, the impact of HIV/HEV coinfection in liver disease is unknown in the country.

Currently, it is unknown what risk factors predispose for coinfections; which HBV, HCV and HEV genotypes circulate in patients infected with HIV and their role in the development of liver disease in specific regions.

Systematic studies and deeper knowledge of HIV coinfection with hepatotropic viruses is required. It is necessary to clarify risk factors, complications and epidemiology, both regional and globally. Altogether will enable clinicians to better handle liver disease.

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